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# Systematic Screening for *Chlamydia trachomatis*: Estimating Cost-Effectiveness Using Dynamic Modeling and Dutch Data

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## ABSTRACT

**Objective:** To estimate the cost-effectiveness of a systematic one-off *Chlamydia trachomatis* (CT) screening program including partner treatment for Dutch young adults.

**Methods:** Data on infection prevalence, participation rates, and sexual behavior were obtained from a large pilot study conducted in The Netherlands. Opposite to almost all previous economic evaluations of CT screening, we developed a dynamic Susceptible-Infected-Susceptible (SIS) model to estimate the impact of the screening program on the incidence and prevalence of CT in the population. SIS models are widely used in epidemiology of infectious diseases, for modeling the transmission dynamics over time. Subsequently, a predictive decision model was used to calculate the complications averted by the screening program. Cost-effectiveness was expressed as the net costs per major outcome averted (MOA) and was estimated in the baseline analysis and in sensitivity analysis.

**Results:** The overall prevalence decreased from 1.79% to 1.05% as a result of the screening program directed at both

men and women. The program costs were mainly offset by the averted costs, although not fully. Resulting net costs per MOA were €373 in the baseline analysis. Sensitivity analysis showed that partner treatment and sending a reminder are important aspects improving cost-effectiveness. Additionally, restricting the screening to women only was estimated to save costs.

**Conclusions:** Our cost-effectiveness analysis shows that the Dutch society has net to pay for the prevention of CT-complications through screening young men and women. One could argue although that €373 per MOA presents a reasonable cost. A screening program consisting of screening women only should always be adopted from a pharmacoeconomic point of view. Our dynamic approach appreciates better the specific characteristics of an infectious disease, such as CT.

**Keywords:** *Chlamydia trachomatis*, cost-effectiveness analysis, screening, transmission dynamics.

## Introduction

Infections caused by the bacteria *Chlamydia trachomatis* (CT) are the most prevalent sexually transmitted infections in industrialized countries, such as in the Netherlands [1]. In women, 70% of these infections remain asymptomatic, which increases the risk of infecting others and may cause long-term complications. Among these complications are pelvic inflammatory disease (PID), chronic pelvic pain (CPP), ectopic pregnancy, and infertility [2–4]. Vertical transmission from mother to child may lead to conjunctivitis and pneumonia [5]. These serious complications are accompanied by major individual and societal costs; total costs for sexually transmitted diseases (STDs) in The Netherlands have been estimated at €25 million,

with CT being the most important Dutch STD currently (<http://www.rivm.nl/kostenvanziekten>).

Screening programs have become more feasible with the introduction of sensitive DNA detection methods, such as the polymerase chain reaction (PCR) test on urine, and the highly effective single-dose azithromycin treatment [6,7]. Active case finding and early treatment can prevent the development of sequelae and the transmission of the disease in the population. CT screening of young persons, especially women, is recommended in several countries including Sweden and the United States [8,9]. In The Netherlands, the issue whether or not to implement a national screening program is under discussion, as is currently the case in other countries such as the UK.

When considering implementing a screening program cost-effectiveness is an important factor to take into account. Many cost-effectiveness analyses have evaluated the costs and health outcomes of both opportunistic and systematic screening programs with and without partner treatment [10–17]. Except three studies [16–18], all of these cost-effectiveness analyses

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were based on static models. Nevertheless, because CT is a transmissible infectious disease the spread of the disease over time in the population should ideally be taken into account. Consequently, more valid results may be expected if a dynamic model is used instead of a static one [19].

In this article we used a dynamic model to estimate the cost-effectiveness of a one-off systematic CT screening program including subsequent (partner) treatment among 15- to 29-year-old men and women. Our approach builds on a previous model that was published in this journal [12]. In particular, the static approach presented previously to evaluate partner treatment is extended into a dynamic one. Additionally, our approach builds on data gathered within the context of a recently performed pilot study on CT screening in The Netherlands [20]. These data involve, for example, participation in the screening, asymptomatic infections detected, sexual behavior and a cost analysis. Summarizing, our current analysis combines an epidemiologic and cost analysis of a Dutch screening program into a model to estimate downstream health gains and related savings on health-care costs.

## Methods

In this section we elaborate on the data and the model used for the cost-effectiveness analysis. The model consists of a dynamic epidemiologic part and an economic part. The epidemiologic part was used for estimating the impact of the screening program on the incidence and prevalence of CT in the population. The economic part addresses the averted complications and averted costs and the cost analysis of the screening program. Both models were linked by using the output of the epidemiologic part as input for the economic analysis to estimate cost-effectiveness.

## Data

Data were used from a pilot study of systematic one-off CT screening in four regions in The Netherlands organized via the Municipal Public Health Services [20]. The study population consisted of 21,000 males and females from the general population aged 15 to 29 years. The sampling method is comprehensively described elsewhere [20]. The selected persons received a package by mail containing a urine sampling kit. Returned urine samples were pooled by five and tested for the presence of chlamydial DNA by means of PCR. Persons who tested CT positive received a referral letter for a health-care provider. It was recommended to treat current partners together with the index case. Partner referral for investigation and/or treatment for all partners of the previous 6 months was recommended and registered. A prevalence of CT infection of 2% was found [20]. For calibrating our model (see *Dynamic Epidemiologic Model*) screening test preva-

lence was corrected for sensitivity and specificity of the CT test, assumed at 98.8% and 99.9%, respectively [21]. This procedure rendered a corrected prevalence of 1.79%.

## Dynamic Epidemiologic Model

We used a deterministic SIS model, in which individuals who are Susceptible can be Infected after which they return to the Susceptible class on recovery. SIS models are widely used in exploring the transmission dynamics of infectious diseases [22]. The model is described in detail in the Appendix. The model describes a heterosexual population of 100,000 man and women with a sex ratio 1:1 and a uniform age distribution over 15 to 29 years. People (15-year-olds) who enter the model exactly balance the people (30-year-olds) who leave the model. The population was divided according to gender, level of sexual activity (core and noncore), and condition (susceptible, symptomatically infected or asymptotically infected). Persons in the pilot study who reported sexual intercourse with two or more different partners in the last half year were denoted as the core group although the others are denoted as the noncore group. As a consequence of the stratification by sexual activity an assumption about the mixing of the subpopulations is required. We used the mixing structure to calibrate the model on the corrected prevalence allowing all structures from full proportionate mixing to full preferred mixing within one's own sexual activity group only (see Appendix) [23,24].

We assumed that before the implementation of the screening program the infection has reached endemic equilibrium. So, in absence of any perturbations the incidence and prevalence are not changing over time (Appendix). The parameter values used in the epidemiologic model are shown in Table 1 [25–28]. These values were derived both from literature and the pilot study.

The systematic screening program targeting 15- to 29-year-old males and females containing treatment of index cases and (ex-)partners of the last 6 months was integrated in the epidemiologic model at time,  $t = 0$  (Appendix). Of all eligible persons 47% of the women and 33% of the man sent in urine [20]. Of the positive index cases 90% were treated. Moreover, 43% of the partners of male index cases (80% of them current, 20% of them ex) were treated (confirmed) compared with 51% of partners of female index cases (98% of them current, 2% of them ex) [30]. Effectiveness of azithromycin was assumed to be 95% [7]. Furthermore, in the baseline analysis, we assumed that only half of the complications were averted in those cases averted as a direct result of the screening program at  $t = 0$  [31]. Because the infections were already present before  $t = 0$  they already could have caused damage.

**Table 1** Parameter values used in the epidemiologic model

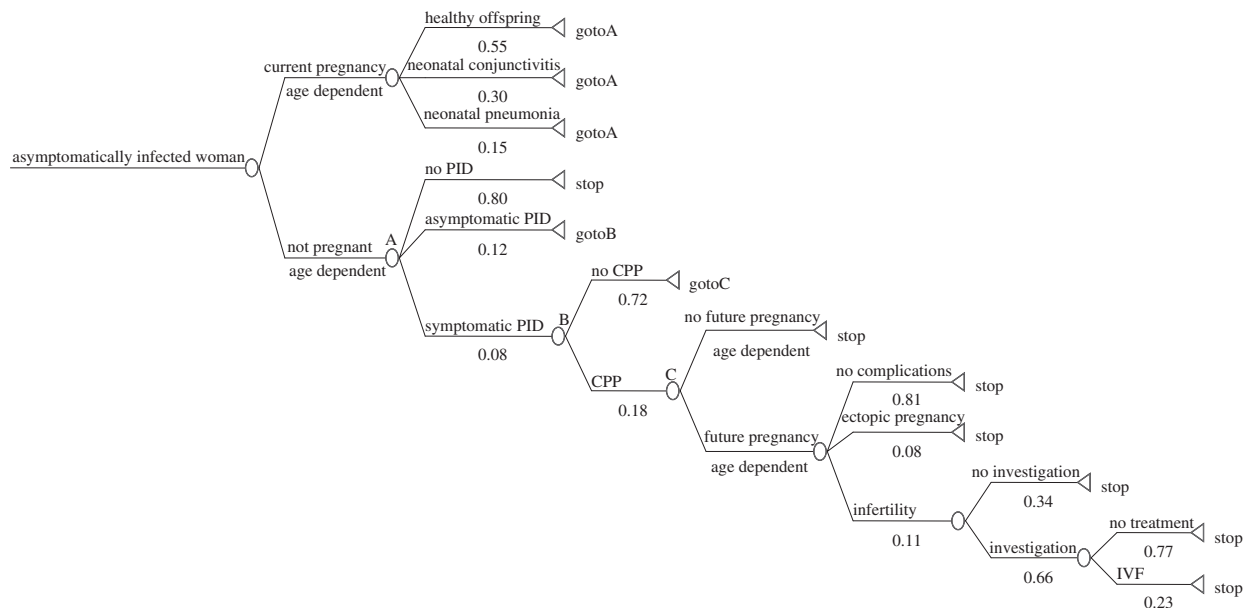
Parameter	Value	Reference(s)
Number of people*		
N <sub>1</sub> (men, core)	0.056 N <sub>total</sub> <sup>†</sup>	PILOT
N <sub>2</sub> (women, core)	0.041 N <sub>total</sub> <sup>†</sup>	PILOT
N <sub>3</sub> (men, noncore)	0.444 N <sub>total</sub> <sup>†</sup>	PILOT
N <sub>4</sub> (women, noncore)	0.459 N <sub>total</sub> <sup>†</sup>	PILOT
Average number of partners per individual per half year*		
a <sub>1</sub> (men, core)	4.23	PILOT
a <sub>2</sub> (women, core)	3.89	PILOT
a <sub>3</sub> (men, noncore)	0.66	PILOT
a <sub>4</sub> (women, noncore)	0.79	PILOT
Transmission probability		
Transmission probability without condom use	0.68	[21]
q <sub>c</sub> (transmission probability, core)	0.41	
q <sub>n</sub> (transmission probability, noncore)	0.55	
Symptomatic infections		
p <sub>m</sub> proportion symptomatic infections male	0.5	[22]
p <sub>f</sub> proportion symptomatic infections female	0.3	[22]
Recovery rate (per year)		
v <sub>a</sub> (asymptomatic infections)	1.0	[23]
v <sub>s</sub> (symptomatic infections)	12.0	[24]
"Influx/efflux" rate (per year)		
μ	1/15	Model assumption

\*Rounded figures; as partnerships closely balance (estimated total number of male contacts are 52,992 for N<sub>total</sub>; female 52,210), no adjustment for using these figures in the model is required [29]; <sup>†</sup>N<sub>total</sub> = 100,000.

### Economic Model

**Progression of disease.** A progression-of-disease tree was used to calculate the complications in the presence and absence of the screening program, related to the incidences of asymptomatic infections in both cases. Figure 1 reflects this progression tree for women and the accompanying probabilities that describe the disease progression of asymptomatic infected persons. The progression tree for men was simply assuming

epididymitis in 2% of asymptotically infected persons without any further complications. Symptomatic CT infections (cervicitis and male urethritis) were assumed to be treated without complications and no further progression of disease was taken into account [17–19]. Without screening every asymptotically infected person enters the progression-of-disease tree, with screening the entrance is limited according to the effectiveness of the screening specified above. The



**Figure 1** Tree for the disease progression of asymptotically infected persons (IVF, in vitro fertilization), probabilities used in the baseline analysis are indicated.

probabilities, except the probability of developing PID, were obtained from a review of the current literature [12,16]. The probability of developing a PID after being infected was estimated at 0.20 [12,16,31,32]. Because the probabilities of being pregnant and desiring future pregnancy are age-dependent, the probabilities of pregnancy-related sequelae of CT infection are age-dependent as well. The probabilities of vertical transmission resulting in neonatal conjunctivitis and pneumonia and of having an ectopic pregnancy were estimated using overall birth rates in The Netherlands [33]. In particular, overall birth rates were interpreted indicating the proportion of women being pregnant during a year. For the probability of being identified as infertile only the birth rates of the first children were used. For this purpose, birth rates of first children were interpreted as indicating the proportion of women having a pregnancy wish. Future outcomes averted were discounted at a rate of 4% per year in the baseline analysis. Complications in newborn and developed PID were assigned to the year of infection. It was assumed that CPP occurs 5 years after PID.

*Averted costs.* Because the complications of a CT infection may involve the use of medical resources and the loss of productivity time, monetary benefits were achieved by the screening program. Our analysis was performed using the societal perspective: both the averted direct medical costs (irrespective of reimbursement issues) and the indirect costs of production losses were included in the analysis as shown in Table 2 [34].

**Table 2** Estimates of undiscounted direct and indirect medical costs used as inputs for the cost-effectiveness model (2002 euros; source: [12]), proportions of patients using inpatient and outpatient care are indicated between brackets

Complication*	Direct costs	Indirect costs <sup>†</sup>
Symptomatic PID		
Inpatient treatment (0.25)	4,085	292 (672)
Outpatient treatment (0.75)	70	139 (320)
CPP		
Inpatient treatment (0.30)	3,460	292 (672)
Outpatient treatment (0.70)	614	139 (320)
Ectopic pregnancy	3,040	896 (896)
Infertility investigation		
Inpatient treatment (0.20)	2,420	224 (224)
Outpatient treatment (0.80)	841	303 (303)
In vitro fertilization	3,138	421 (421)
Neonatal conjunctivitis	41	Not applicable
Neonatal pneumonia		
Inpatient treatment (0.10)	16,882	Not applicable
Outpatient treatment (0.90)	98	Not applicable
Epididymitis		
Inpatient treatment	2,123	286 (891)
Outpatient treatment	86	143 (445)
Male urethritis	46	10 (30)
Cervicitis	46	8 (15)

\*Probabilities of inpatient and outpatient treatment are in parentheses [11]; <sup>†</sup>Indirect costs are shown for persons aged 15 to 24 (for persons aged 25 to 29 indirect costs are in parentheses).

CPP, chronic pelvic pain; PID, pelvic inflammatory disease.

**Table 3** Estimated direct costs of the screening program by category in 2002 euros (for one category of indirect costs and savings on returned packages see text)

	Costs
Implementation of the program	660,000
Package	3.50
Sending a reminder	0.68
PCR test	12
Sending results	0.49 (0.59*)
General practitioner visit*	17.50
Treatment (azithromycin)*	7.55
Prescription fee*	6

\*For persons with a positive test only.

PCR, polymerase chain reaction.

The cost estimates were updated from the research previously published by Postma et al. in this journal [12], by converting them to 2002 prices using gross domestic product deflators [35]. Future costs were discounted at a rate of 4% per year in the baseline analysis according to the Dutch guidelines for pharmacoeconomic research [34].

*Cost analysis of screening.* Program costs that were taken into account consist of the costs associated with screening, subsequent (partner) treatment and the implementation of the program. All program costs were derived from the pilot study. Estimated costs of €660,000 for the implementation of the program were based on the workload reported by the participating agencies adjusted for population size. These costs do not depend on the prevalence. The screening and treatment costs do depend on the prevalence. The whole study population received a package by mail containing a urine sampling kit, introductory letter and information leaflet on CT with a total cost of €3.50 a piece. Nonresponders received a reminder (67,000) after 6 weeks at a cost of €0.68. All packages returned (41%) yielded €1.22 because of potential reuse of the package. Urine samples were pooled by five and tested by PCR with a cost of €12 per test including labor and laboratory costs. All participants received their test result by mail at a cost of €0.49 and those tested positive also received a referral letter for the health-care provider (extra €0.10). It was assumed that 90% of the positive cases visited a general practitioner, consisting of both direct (€17.50) and indirect costs, and received an azithromycin prescription at a cost of €13.55 (inclusive the prescription fee for the pharmacist). In the pilot study there were different ways of treating the (ex-)partner. Here it was assumed that current partners were treated together with the index by the same health-care provider, resulting in an extra prescription. Ex-partners received a referral letter for the health-care provider and were assumed to visit a GP. All screening-related costs are listed in Table 3.



### Modeling Cost-Effectiveness

The dynamic epidemiologic and the economic models were linked together by using the output of the epidemiologic model in terms of annual symptomatic and asymptomatic CT-cases as input for the economic model. In the economic model these incidences were followed with respect to complications (Fig. 1) and the related resource use and costs (Table 2) in both situations investigated in the incremental analysis: no screening versus screening. In the latter case also the screening costs (Table 3) were included. The differences between both options resulted in the net costs (savings) for screening and the averted complications through screening, combined in the incremental cost-effectiveness ratio in euros per disease outcome averted (i.e., health gain).

In particular, we expressed cost-effectiveness as the net costs per major outcome averted (MOA) and as net cost per PID averted [36–38]. Symptomatic PID, CPP, ectopic pregnancy, infertility, and neonatal pneumonia were considered major outcomes and were aggregated into one figure. Because several major outcomes may occur in one patient, additionally PID was analyzed as separate outcome because this complication is conditional for many others (Fig. 1). Cost-effectiveness is presented in a baseline analysis as well as a sensitivity analysis. The parameter values introduced above are used in the baseline analysis. A period of 10 years was chosen for analyzing the impact of the screening program on the CT incidence and prevalence in the population. Complications and related costs for cases in these 10 years were included in the model, despite the fact that complications may take place beyond this period. A period of 10 years was chosen to fully acknowledge the dynamics of our approach within a still reasonable time frame to produce plausible results. Beyond 10 years one may assume that various influencing factors have significantly changed in the meantime, rendering our results potentially invalid.

A univariate sensitivity analysis was performed for all uncertain parameters to test the robustness of the outcomes of the analysis. The baseline parameter values for probability of PID, recovery rate of asymptomatic infections, percentage complications averted at  $t = 0$ , PCR test costs and discount rate were varied over plausible ranges (as derived from previous research [12,16]) to explore the impact of different parameter values on the results.

A limitation of the SIS model used is the difficulty to model the regular partner treatment (both before and after  $t = 0$ ). Generally, regular partner treatment concerns asymptomatically infected current partners of symptomatic index cases who visit a general practitioner. These partners are subsequently treated and recover quickly. In the baseline analysis regular partner treatment was not modeled (recovery rate  $v_a$  equals 1

for all asymptomatic cases). In the sensitivity analysis we did investigate the impact of including regular partner treatment on the cost-effectiveness by assuming a higher recovery rate for asymptomatic infections throughout the model ( $v_a = 1.2$ ) as a result of this regular partner treatment.

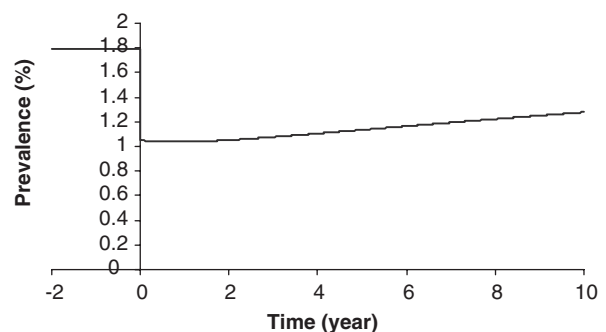
Moreover, the following scenarios were investigated: 1) screening women only; 2) absence of any partner treatment; 3) not sending a reminder; and 4) treating 56% (85% current, 15% ex) and 68% (95% current, 5% ex) of the partners of, respectively, the male and female index cases (these percentages include confirmed and probable partner treatments in the pilot study CT [20, 30]).

### Results

The steady state prevalence's by sexual activity and gender obtained with the dynamic model closely agree with the corrected prevalences. For the male core group we obtained a corrected prevalence and a model prevalence of 5.1% and 6.3%, respectively, whereas for the noncore group the prevalences (1.0%) exactly match. Regarding females, we obtained a corrected prevalence of 7.2% and a model prevalence of 8.4% for the core group and a corrected prevalence of 1.7% and a model prevalence of 1.4% for the noncore group. The mixing structure to obtain the estimated overall prevalence of 1.79% was close to proportionate mixing. The exact mixing structure is provided in the Appendix.

#### Baseline Analysis

The one-off screening program reduces the CT prevalence in the whole population as shown in Fig. 2. The overall prevalence drops from 1.79% before to 1.05% after the screening (at  $t = 0$ ), after which it takes a long period to reach the steady state prevalence again. Indeed, if after the intervention there would be no mixing between the different sexual activity groups anymore, eradication of CT in the noncore groups is achieved (results not shown). Ergo, a certain level of



**Figure 2** *Chlamydia trachomatis* prevalence in the whole population before (steady state) and after the intervention ( $t = 0$ ).

**Table 4** Outcomes of the incremental analysis in the baseline and sensitivity analysis for a population of 100,000 persons (costs in 2002 euros)

	No screening		Screening			
	Costs complications	Major outcomes (PIDs)	Screening costs	Costs complications	Major outcomes (PIDs)	Cost/MOA (cost/PID averted)
Baseline analysis	2,754,059	1217 (1658)	1,212,778	1,714,750	752 (1024)	373 (274)
Sensitivity analysis						
Probability PID 0.15	2,259,408	927 (1244)	1,212,778	1,409,126	573 (768)	1023 (763)
Probability PID 0.10	1,764,758	638 (829)	1,212,778	1,103,502	394 (512)	2261 (1741)
Probability PID 0.25	3,248,709	1506 (2073)	1,212,778	2,020,374	930 (1281)	-27 (-20)
$v_s = 1.2$	3,242,786	1424 (1940)	1,212,778	2,084,756	906 (1235)	106 (78)
Complications averted at $t = 0, 0\%$	2,754,059	1217 (1658)	1,212,778	1,770,163	782 (1066)	527 (386)
Complications averted at $t = 0, 100\%$	2,754,059	1217 (1658)	1,212,778	1,659,337	721 (983)	238 (175)
Only direct costs	2,246,111	1217 (1658)	1,204,093	1,397,804	752 (1024)	765 (562)
Cost PCR test €24	2,754,059	1217 (1658)	1,308,658	1,714,750	752 (1024)	579 (425)
Discounting 3%	2,942,713	1298 (1727)	1,212,778	1,838,089	805 (1071)	219 (165)
Discounting 5%	2,584,433	1143 (1594)	1,212,778	1,604,006	704 (981)	529 (379)
Discounting effects 0% (costs 4%)	2,754,059	1354 (1768)	1,212,778	1,714,750	757 (1035)	291 (237)
Screening females only	2,754,059	1217 (1658)	669,077	2,035,271	895 (1220)	-154 (-113)
Without reminder	2,754,059	1217 (1658)	1,141,108	1,899,135	834 (1137)	748 (549)
No partner treatment	2,754,059	1217 (1658)	1,208,660	1,992,425	876 (1194)	1312 (962)
Partner treatment (male index: 56%, female index: 68%)	2,754,059	1217 (1658)	1,214,189	1,619,892	709 (967)	158 (116)

MOA, major outcome averted; PCR, polymerase chain reaction; PID, pelvic inflammatory disease;  $v_s$ , recover rate for asymptomatic infections.

mixing is required between core and noncore groups to sustain CT-transmission in the population.

The investment in screening and (partner) therapy is estimated at €1,212,778 for a population of 100,000 men and women. These program costs are mainly offset by the €1,039,308, which is averted over 10 years by the one-off screening program. So, the screening program is estimated to cost €373 per MOA or €274 per PID averted (Table 4).

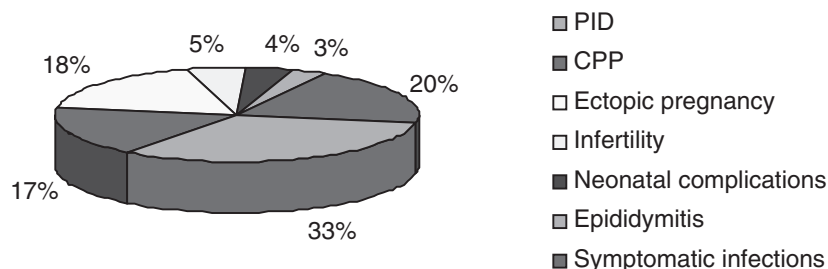
Figure 3 specifies the distribution of the averted costs by disease category. Approximately one-third of the averted costs are a direct result of the prevention of PID. Furthermore, costs of with ectopic pregnancies (18%) and CPPs (17%)—that are indirectly related to PID—and those of symptomatic infections (20%) are substantially responsible for the total costs averted. As can be derived from the figure, MOAs (averted symptomatic PIDs, CPPs, ectopic pregnancies, infertility, and neonatal pneumonias) are responsible for approximately three-quarters of the averted costs. Furthermore, over a 10-year period the one-off screening program in our modeled population of 100,000 persons leads to the prevention of 634 cases of PID, 125 cases of CPP, 86 ectopic pregnancies, 53 infertilities,

75 neonatal complications, 52 cases of epididymitis and 3896 symptomatic infections.

### Sensitivity Analysis

The results of the univariate sensitivity analysis are presented in Table 4. The progression rate to PID is an important model parameter. Varying the rate from 0.10 to 0.25 has a large influence on the outcomes. Reducing the risk to 0.10 results in a 218% increase in the net costs and in, respectively, 48% and 50% reduction in the number of MOAs and PIDs averted. Conversely, assuming a PID risk of 0.25 the program is estimated cost-saving.

By assuming a recovery rate of 1.2 for asymptomatic infections to indirectly model regular partner treatment, the screening program is estimated even more cost-effective (€106 per MOA and €78 per PID averted) than in baseline. Relatively small changes are seen when changing the discount rate to 3% or 5% as is common in other countries or when the health benefits are not discounted at all. Varying the percentage of complications averted as a direct result of the screening program ( $t = 0$ ) between 0 and 100%, and doubling the test costs only had limited influence on



**Figure 3** Percentage distribution of costs by disease category averted by the screening program. CPP, chronic pelvic pain; PID, pelvic inflammatory disease.

the outcomes as well. Nevertheless, excluding indirect costs of production losses almost doubled the cost-effectiveness ratio.

Partner treatment as well as sending a reminder can be considered as cost-saving interventions within the screening program. Both cause a large decrease in the total net costs and a large increase in the number of major outcomes and PIDs averted. Finally, restricting the screening only to women the program is estimated cost-saving.

## Discussion and Conclusion

Application of our dynamic model shows that the costs of the one-off systematic screening program exceed the benefits of averted health care under baseline assumptions; society has net to pay for the prevention of CT complications. Cost-effectiveness was estimated at €373 per MOA and €274 per PID averted in the baseline analysis. We estimated that the overall prevalence would initially decrease to 1.05% as a result of the screening program. The core group maintains infection in the population and as a result of somewhat restricted mixing between core and noncore groups the infection takes more than 10 years to reach again the previous steady state prevalence in the population as a whole (Fig. 2).

Our sensitivity analysis has illustrated that both partner treatment and sending a reminder are cost-saving activities within the screening program; these activities improve overall cost-effectiveness. The importance of partner referral has been demonstrated before [12]. Obviously, it depends on the number of responders whether or not sending a reminder is cost-effective. Also, the sensitivity analysis revealed limited impact for varying the discount rate. This may be explained by the facts that: 1) the screening costs are insensitive to discounting because they occur at the beginning of the analysis only; and 2) the vast majority of complications (costs) are averted in the first 5 years of our 10-year time frame (Fig. 2).

There are several limitations of our study. One general limitation inherent to mathematical models is that the validity of the results strongly depends on the precision of the parameter estimates [39]. Data on sexual behavior and the screening program were obtained from the pilot study whereas data on the natural course of a CT infection were derived from clinical trials (Table 1). The sensitivity analysis shows that the risk of developing PID has a large impact on the cost-effectiveness of the screening program. Unfortunately, different studies have quantified the risk of PID differently [31, 32, 40], so there is still a debate on the exact risk. Because this parameter value has such a large influence on the outcomes future research is required to exactly determine the risk of developing PID. Furthermore, the model assumes a population with a uni-

form age and sex distribution where no migration occurs and also the assumption of a stable-steady state prevalence over time may not hold. Nevertheless, obviously any model should be a simplification of reality to an acceptable degree. Also, we implicitly assumed that no selection occurs in participating in the screening, that is, prevalence is similar in those participating and those not participating in the screening. Finally, we note that our model renders the prevalence found in the investigated population, which does obviously not guarantee that also the predicted prevalence is valid. External validation of the model is needed, however, data are yet lacking.

Our SIS model differs from a network model, as developed, for example, by Kretzschmar et al. [16,41]. Ours is deterministic and population-based, whereas the one developed by Kretzschmar et al. is stochastic and individually based. The advantage of the network approach is that it is very detailed and potentially very realistic. For instance, a network approach would easily allow for modeling recurrent and persistent infection, which is not included in our current approach. Furthermore, partner notification can explicitly be modeled and it is possible to assume an increased risk of complications in those who have been reinfected. Nevertheless, the data requirements are much more extensive for such a network model, in particular regarding data on sexual behavior. Unfortunately, limitations definitely apply to the availability of accurate data on sexual behavior hampering the use of stochastic network models. We dealt with this scarce availability of accurate data on sexual behavior by calibrating the model with the mixing matrix on the corrected test prevalence.

The design of the SIS model confronted us with a difficulty to model the regular partner treatment (i.e., before and after  $t = 0$ ). In the sensitivity analysis we indirectly assessed the influence of including regular partner treatment on the cost-effectiveness. It is shown that an increase in the recovery rate for asymptomatic infections decreases the costs per MOA and per PID averted. So, if partner treatment is current practice the screening program becomes more cost-effective. Furthermore, our estimate of cost-effectiveness may be too conservative for another reason. The impact of CT on the susceptibility for other STDs (e.g., HIV) was not taken into account; CT increases the susceptibility for other STDs [42].

The use of a dynamic model—such as the SIS model—to estimate the cost-effectiveness of a CT screening program has major advantages. Until now, a static approach has been the standard for determining the cost-effectiveness of CT screening programs. Nevertheless, as with all infectious diseases, it is very important to take the transmission dynamics of CT into account to not (hugely) overestimate the cost-effectiveness ratio and underestimate attractiveness of



the program. In particular, a static approach would not consider benefits and health gains beyond the immediate effect of the screening. Of our averted costs and major outcomes, 93% and 94% are beyond this immediate effect, respectively.

Policy impact of our application of the dynamic approach may be that CT screening is more and more seen as a cost-effective intervention. Inclusion of the dynamic effects of such a screening greatly enhances the health-economic profile of this intervention. Currently, in The Netherlands, interventions are valued with respect to the "official" cutoff point for cost-effectiveness/cost-utility at €20,000 per life-year gained or quality-adjusted life-year (QALY) [43]. A crude assessment of the cost-utility of our analysis is possible using recently published QALY weights for the US situation: 0.90 (during 4 weeks) for symptomatic infection, 0.65 (during 11 days) for symptomatic PID, 0.60 (during 5 years) for CPP, 0.58 (during 4 weeks) for ectopic pregnancy and 0.82 (during the rest of life until age 50) for infertility [18]. Inclusion of these estimates in our model with baseline assumptions renders a cost-utility below €1000/QALY, obviously warranting adoption given the above specified threshold. Obviously, this crude assessment is only indicative and requires further research to validate QALY weights for the Dutch population.

In conclusion, we have shown that the prevention of one major outcome as a result of the screening program costs €373 for the Dutch situation. One could argue that this is a reasonable cost for preventing a major outcome (e.g., infertility). There exist several other prevention programs where society has net to pay for the prevention of complications due to infectious diseases [44,45]. A screening program consisting of screening women only and subsequent partner treatment should always be adopted from a pharmacoeconomic point of view because it is a cost-saving activity (Table 3). Nevertheless, cost-effectiveness is not the only aspect to consider before implementation, others being, for example, ethical, budgetary, and organizational aspects.

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## Appendix

### SIS Model

The population was divided into four different groups according to gender and sexual activity level. Furthermore, each different group can be divided into three different classes according to the condition (symptomatically infected, asymptotically infected or susceptible). Consequently, this results in a division into 12 different classes. These 12 different classes can be described by a system of 12 nonlinear ordinary differential equations. The three general equations are given by:

$$\begin{aligned}\frac{dI_{s_i}}{dt} &= (\lambda_{ij}I_j(t) + \lambda_{i(j+2)}I_{j+2}(t))\frac{S_i(t)}{N_i}p_i - I_{s_i}(t)v_s - \mu I_{s_i}(t) \\ \frac{dI_{a_i}}{dt} &= (\lambda_{ij}I_j(t) + \lambda_{i(j+2)}I_{j+2}(t))\frac{S_i(t)}{N_i}(1-p_i) - I_{a_i}(t)v_a \\ &\quad - \mu I_{a_i}(t) \\ \frac{dS_i}{dt} &= \mu N_i - (\lambda_{ij}I_j(t) + \lambda_{i(j+2)}I_{j+2}(t))\frac{S_i(t)}{N_i} + I_{s_i}(t)v_s \\ &\quad + I_{a_i}(t)v_a - \mu I_{s_i}(t)\end{aligned}$$

The demographic and epidemiologic parameters in these equations are:

$t$  = time,

$I_{s_i}$  = number of symptomatically infected in group  $i$ ;

$I_{a_i}$  = number of asymptotically infected in group  $i$ ;

$S_i$  = number of susceptible in group  $i$ ;

$\lambda_{ij}$  = contact rate, average number of contacts resulting in infection per unit time of an infective in group  $j$  with persons in group  $i$ . The contact rate is defined by:

$m_{ij}a_jq_j$ ;

$m_{ij}$  = the proportion of partners by an average infective of group  $j$  in group  $i$ ;

$a_j$  = average number of partners per unit time of persons in group  $j$ ;

$q_j$  = transmission probability with condom use taken into account;

$p_i$  = proportion symptomatic infections (gender-specific);

$v_s$  = per capita recovery rate for symptomatic infections;

$v_a$  = per capita recovery rate for asymptomatic infections;

$\mu$  = the “influx/efflux” rate.

The values used for these parameters in the model are shown in Table 1. It was assumed that  $q_i = q_c$  if  $i = 1$  and  $j = 2$ , and  $q_j = q_c$  otherwise (see Table 1).

Because the population is stratified by sexual activity it is required to make an assumption about the mix-

ing of the subpopulations. We adapted the so-called proportionate mixing assumption; a commonly made assumption that states the subpopulation mixes randomly, but weighted with their sexual activity [22–24]. For proportionate mixing holds that  $m_{ij} = a_i N_i / A$ ,

where in general  $A = \sum_{i=1}^n a_i N_i$ . Whereas a member of

the core group may be more likely to have sexual intercourse with a member of the core group the proportionate mixing assumption is not completely reasonable. So, we used a mixing matrix  $M = [m_{ij}]$  that is  $C$  times the mixing matrix for proportionate mixing and  $C-1$  times the mixing matrix for solely mixing within the two sexual activity classes. The last matrix is filled solely with zero's and one's.

### Steady State

Before the screening program we assumed a steady state so that there was no time dependence in the incidence and prevalence. In other words the 12 differential equations were set to zero:  $dI_{s_i}/dt = 0$ ,  $dI_{a_i}/dt = 0$ , and  $dS_i/dt = 0$ . Subsequently, these equations were solved to obtain the prescreening equilibrium number of symptomatically infected, asymptotically infected and susceptible. We varied the mixing structure to calibrate on the estimated real overall prevalence in the pilot study (1.79%). The best fit was acquired with a  $C$  of 0.86, which gave the mixing matrix  $M$  as shown below:

$$M = [m_{ij}] = \begin{pmatrix} 0 & 0.53 & 0 & 0.39 \\ 0.41 & 0 & 0.26 & 0 \\ 0 & 0.47 & 0 & 0.61 \\ 0.59 & 0 & 0.74 & 0 \end{pmatrix}$$

### Screening Program

For the entire population it was assumed that screening and partner treatment took place at one and the same point in time ( $t = 0$ ). In general, the number infected is decreased as a result of the screening program as shown by:  $I_{t=0} = I_{\text{steady state}} - (A + B)$  where  $A$  and  $B$  represent the efflux as a result of screening and partner referral, respectively. First, the number recovered as a result of screening ( $A$ ) can be represented as:  $I_{\text{steady state}} \times \text{proportion screened} \times \text{test sensitivity} \times \text{proportion treated} \times \text{effectiveness azithromycin}$ . As an example we provide the efflux due to the screening program in the male, noncore, and symptomatically infected class ( $I_{s_1}$ ):  $A = 28.65 \times 0.334 \times 0.988 \times 0.9 \times 0.95 = 8.08$ .

Nevertheless, the estimation of the efflux as a result of partner referral is much more complex. People can only be treated as a result of partner referral as a partner (index) in the last half year is tested positive. Positive tested index cases consist of true positives and false positives. The partners (index cases) can be divided into three categories: partners before infection,

partners after infection, and the infector who transmitted the infection. We return to the example to clarify the above. An asymptomatic infected person on average got infected half a month ago because the recovery rate is 12. The probability that the infector was symptomatically infected is 0.04 and that she was asymptotically infected was 0.96. The probability that the infector still is infected at  $t = 0$  is  $23/24$  for asymptotically infected infectors and  $1/2$  for symptomatically infected infectors. So, the overall probability of the infector still being infected at  $t = 0$  is  $0.04 \times 23/24 + 0.96 \times 1/2$ , that is, 0.94. The number of partners after being infected is 0.35 ( $= a_1/12$ ) of who 0.14 ( $= 0.35 \times q_c$ ) are infected at  $t = 0$ . Finally, the number of partners before getting the infection is 2.88 ( $= a_1 - a_1/12 - 1$ ). The probability for them still being infected at  $t = 0$  is 0.04, which directly results from the mixing matrix and the prevalence. Summarizing, the above results in 1.21 ( $0.94 + 0.14 + 2.88 \times 0.04$ ) infected and 3.03 ( $= a_1/2 - 1.21$ ) noninfected partners

per symptomatically infected male member of the core group. Subsequently, the number of true positives ( $=$  number of partners in the past half year who are infected  $\times$  test sensitivity  $\times$  proportion screened of opposite sex) and the number of false positives ( $=$  number of partners in the past half year who are not infected  $\times$   $[1 - \text{test specificity}] \times$  proportion screened of opposite sex) are estimated to be 0.55 and 0.00, respectively. Because current partners were epidemiologically treated together with the index and ex-partners were tested before treating the efflux as a result of partner referral (B) becomes:  $(28.65 - 28.65 \times 0.33) \times [(0.55 + 0.00) \times \text{proportion partners treated} + [\text{proportion current partners} \times \text{proportion treated} + \text{test sensitivity} \times \text{proportion ex-partners}]]$ . In this example B is estimated to be 4.63, which results in an  $I_{t=0}$  of 15.94 what means that 12.71 symptomatically infected male members of the core group are cured as a direct result of the screening program and return to the susceptible class.